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10/556,123	11/09/2005	Steffen Panzner	56362.4	4731

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,123	PANZNER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 19-43* is/are pending in the application.

4a) Of the above claim(s) *2,23-34 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,19-22,35 and 37-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 3/4/09 was entered.

Amended claims 1-6, 19-37 and new claims 38-43 are pending in the present application.

Applicants elected previously with traverse of Group I, drawn to a depot system containing one or more protein or peptide active substances, a drug comprising the same depot system and **the first method** of using the same depot system by injecting the depot system subcutaneously or intramuscularly, in the reply filed on 2/20/2000. Applicant further elected the following species: (a) DPPC as a species of saturated synthetic phosphatidyl choline; (b) DC-Chol as a species of a cationic lipid; and (c) LHRH agonists as a species of protein and peptide active substances.

Claims 26-34 and 36 were withdrawn previously from further consideration because they are directed to non-elected inventions. Additionally, claims 2 and 23-25 were withdrawn previously from further consideration because they are directed to non-elected species.

This application contains claims 26-34 and 36 drawn to an invention nonelected with traverse in the reply filed on 2/20/2000. **A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.**

Therefore, claims 1, 3-6, 19-22, 35, 37 and new claims 38-43 (to the extent of previously elected invention) are examined on the merits herein with the above elected species.

Examiner's Remark

Should Applicants desire a clear and concise prosecution history of the present application, please point out the specific page number and/or line number in the originally filed specification that provide support for claim amendments, rather than using a generic statement "no new matter and find support in the originally filed specification and claims".

Claim Objections

New claim 38 is objected to because of the phrase "comprising the steps of". This is because there is only a single step of providing liposomes in the claimed method. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical

Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

New claims 38, 40 and 42 are rejected under 35 U.S.C. 102(e) as being anticipated by Gregoriadis et al. (US 7,008,791). ***This is a new ground of rejection necessitated by Applicant's amendment.***

Gregoriadis et al already disclosed at least a liposome preparation comprising at least a cationic compound such as DOTAP or DC-Chol (col. 2, line 65 continues to line 9 of col. 3; col. 3, lines 45-61), at least one zwitterionic phospholipid such as DPPC and DSPC (col. 3, line 62 continues to line 15 of col. 4), and cholesterol, wherein the amount of cationic compound is preferably in the range of 5 to 50% of the total moles of liposome forming components, preferably in the range 10 to 25% mole and the cholesterol is in amounts up to 50% by weight (col. 4, line 16 continues to line 26) to entrap a DNA encoding an antigen, an active substance (see at least the abstract). Gregoriadis et al further taught that the product liposomes may be multilamellar or unilamellar vesicles, and the small vesicles have average diameters in the range 200 to 300 nm (col. 4, lines 27-38). Gregoriadis et al also disclosed that a nucleic acid may be complexed with liposomes, that is located externally of the liposomes, preferably the nucleic acid is at least partially entrapped (col. 4, lines 39-42). Exemplified liposome preparations include a liposome comprising 32 umoles of DSPC, 16 umoles of cholesterol and 8 umole of DOTAP (example 1, preparation 3); 32 umoles of DSPC, 16

umoles of cholesterol and 8 umoles of DC-Chol col. 8, lines 20-23). Gregoriadis et al further taught that the liposome compositions have been found to be resistant to bile salts and this correlates with stability at least in the GI tract (col. 5, lines 39-41) and a method of using the disclosed liposome preparation (col. 5, lines 49-56 and issued claims).

The teachings of Gregoriadis et al meet every limitation of the instant claims as written. Therefore, the reference anticipates the instant claims.

New claims 38-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Unger et al. (US 5,770,222). ***This is a new ground of rejection necessitated by Applicant's amendment.***

With respect to the elected invention and species, Unger et al already disclosed a drug delivery system comprising gas-filled liposomes having encapsulated therein a therapeutic drug, wherein at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied (see at least the abstract; Summary of the Invention; col. 4, line 61 continues to line 27 of col. 5; col. 7, lines 8-13, lines 24-32). Unger et al also taught that **the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation**, and the lipid in the gas-filled liposomes may be in the form of a single bilayer or a multilamellar bilayer and that utilized lipids to create liposome

microspheres include and not limited to: lipids such as dimyristoylphosphatidylcholine (DMPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), cholesterol, cholesterol sulfate and cholesterol hemisuccinate and if desired a variety of cationic lipids such as DOTMA, DOTAP can also be used, wherein in general the molar ratio of cationic lipid to non-cationic lipid in the liposome may be between 2:1 to 1:10 (col. 7, line 42 continues to line 53 of col. 8). Unger et al also disclosed that any of a variety of therapeutics may be encapsulated in the liposomes, including leuprolide acetate, growth hormones, peptides such as manganese super oxide dismutase, enzymes such as alkaline phosphatase, monoclonal antibody, and genetic materials including nucleic acids, DNA and RNA (col. 9, line 30 continues to line 34 of col. 11). Unger et al further disclosed that for intravascular application, the liposome microspheres can be about 30 nm in mean outside diameter (col. 15, lines 12-13); for providing therapeutic delivery to organs liposome microspheres between about 30 nanometers and about 100 nanometers in mean outside diameter can be used (col. 15, lines 14-18). Unger et al further taught that the drug delivery system can be administered into a patient using various routes of administration, including subcutaneously, intramuscularly among others (col. 16, lines 31-44).

The teachings of Unger et al meet every limitation of the instant claims as written. Therefore, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-6, 19-22, 35 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. (US 5,770,222) in view of Gregoriadis et al. (US 7,008,791) for the same reasons already set forth in the Office action dated 4/18/08 (pages 4-8). ***The same rejection is restated below.***

Unger et al already disclosed a drug delivery system comprising gas-filled liposomes having encapsulated therein a therapeutic drug, wherein at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied (see at least the abstract; Summary of the Invention; col. 4, line 61 continues to line 27 of col. 5; col. 7, lines 8-13, lines 24-32).

Unger et al also taught that **the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation**, and the lipid in the gas-filled liposomes may be in the form of a single bilayer or a multilamellar bilayer and that utilized lipids to create liposome microspheres include and not limited to: lipids such as dimyristoylphosphatidylcholine (DMPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), cholesterol, cholesterol sulfate and cholesterol hemisuccinate and if desired a variety of cationic lipids such as DOTMA, DOTAP can also be used, wherein in general the molar ratio of cationic lipid to non-cationic lipid in the liposome may be between 2:1 to 1:10 (col. 7, line 42 continues to line 53 of col. 8). Unger et al also disclosed that any of a variety of therapeutics may be encapsulated in the liposomes, including leuprolide acetate, growth hormones, peptides such as manganese super oxide dismutase, enzymes such as alkaline phosphatase, monoclonal antibody, and genetic materials including nucleic acids, DNA and RNA (col. 9, line 30 continues to line 34 of col. 11). Unger et al further disclosed that for intravascular application, the liposome microspheres can be about 30 nm in mean outside diameter (col. 15, lines 12-13); for providing therapeutic delivery to organs liposome micropheres between about 30 nanometers and about 100 nanometers in mean outside diameter can be used (col. 15, lines 14-18). Unger et al further taught that the drug delivery system can be administered into a patient using various routes of administration, including subcutaneously, intramuscularly among others (col. 16, lines 31-44).

Unger et al do not teach specifically the preparation of a liposome comprising saturated synthetic phosphatidyl cholines selected from one or more from the group consisting of DMPC, DPPC and DSPC; cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of DC-Chol, DAC-Chol, DMTAP, DPTAP and DOTAP with a percentage ranging from about 5 to 20 mole-%, and one or more selected from the group consisting of protein and peptide active substances.

However, at the effective filing date of the present application Gregoriadis et al already disclosed at least a liposome preparation comprising at least a cationic compound such as DOTAP or DC-Chol (col. 2, line 65 continues to line 9 of col. 3; col. 3, lines 45-61), at least one zwitterionic phospholipid such as DPPC and DSPC (col. 3, line 62 continues to line 15 of col. 4), and cholesterol, wherein the amount of cationic compound is preferably in the range of 5 to 50% of the total moles of liposome forming components, preferably in the range 10 to 25% mole and the cholesterol is in amounts up to 50% by weight (col. 4, line 16 continues to line 26) to entrap a DNA encoding an antigen (see at least the abstract). Gregoriadis et al further taught that the product liposomes may be multilamellar or unilamellar vesicles, and the small vesicles have average diameters in the range 200 to 300 nm (col. 4, lines 27-38). Exemplified liposome preparations include a liposome comprising 32 umoles of DSPC, 16 umoles of cholesterol and 8 umole of DOTAP (example 1, preparation 3); 32 umoles of DSPC, 16 umoles of cholesterol and 8 umoles of DC-Chol col. 8, lines 20-23). Gregoriadis et al

further taught that the liposome compositions have been found to be resistant to bile salts and this correlates with stability at least in the GI tract (col. 5, lines 39-41).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the teachings of Unger et al by also utilizing a liposome preparation having liposomal components in the ratios taught by Gregoriadis et al above to encapsulate and deliver a therapeutic drug to a patient.

An ordinary skilled artisan would have been motivated to carry out the above modification because the liposome preparation taught by Gregoriadis et al has been demonstrated to be stable and suitable at least for as an oral-based DNA vaccine. It is further noted that Unger et al taught explicitly that the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Unger et al. and Gregoriadis et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 3/4/09 (pages 7-11) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

With respect to the primary Unger reference, Applicants argue basically that the liposomes in the disclosed examples of the reference do not contain cholesterol. Additionally, the reference teaches that the presence of cationic lipids is not mandatory. With respect to the Gregoriadis reference, Applicants argue basically that the liposomes of Gregoriadis are selected to be stable in the GI tract and to efficiently transfect cells and the reference teaches away from the instant claimed invention as the compositions of Gregoriadis are preferably free of cholesterol as disclosed in the specification and the examples. Applicants further argue that there is no motivation to combine the teachings of Unger and Gregoridadis to arrive at the presently claimed invention, and that this particular combination of teachings is a result of hindsight.

First, please note that the teachings of Unger et al are not limited ONLY to the disclosed exemplified examples. Unger et al taught explicitly that **the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation**, and the lipid in the gas-filled liposomes may be in the form of a single bilayer or a multilamellar bilayer and that **utilized lipids to create liposome microspheres include and not limited to: lipids such as dimyristoylphosphatidylcholine (DMPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), cholesterol, cholesterol sulfate and**

cholesterol hemisuccinate and if desired a variety of cationic lipids such as DOTMA, DOTAP can also be used, wherein in general the molar ratio of cationic lipid to non-cationic lipid in the liposome may be between 2:1 to 1:10 (col. 7, line 42 continues to line 53 of col. 8). Additionally, please also see at least issued claims 20 and 30. It is further noted that cationic lipids were clearly used for the preparation of an exemplified liposomal composition (see at least example 2).

Second, there is no teaching away whatsoever by the Gregoriadis reference. Gregoriadis et al disclosed at least a liposome preparation comprising at least a cationic compound such as DOTAP or DC-Chol (col. 2, line 65 continues to line 9 of col. 3; col. 3, lines 45-61), at least one zwitterionic phospholipid such as DPPC and DSPC (col. 3, line 62 continues to line 15 of col. 4), and **cholesterol, wherein the amount of cationic compound is preferably in the range of 5 to 50% of the total moles of liposome forming components, preferably in the range 10 to 25% mole and the cholesterol is in amounts up to 50% by weight** (col. 4, line 16 continues to line 26) to entrap a DNA encoding an antigen (see at least the abstract). Contrary to Applicant's above argument, **exemplified liposome preparations include a liposome comprising 32 umoles of DSPC, 16 umoles of cholesterol and 8 umole of DOTAP (example 1, preparation 3); 32 umoles of DSPC, 16 umoles of cholesterol and 8 umoles of DC-Chol col. 8, lines 20-23)**. The statement "Preferably the liposome forming components are free of cholesterol" simply indicates an alternative preferred embodiment. Gregoriadis et al also stated explicitly **"In all aspects of the invention**

other components may be included in the liposome forming mixture, such as cholesterol, in amounts up to 50% by weight" (col. 4, lines 16-18.

Third, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As already set forth in the above rejection, an ordinary skilled artisan would have been motivated to modify the teachings of Unger et al by also utilizing a liposome preparation having liposomal components in the ratios taught by Gregoriadis et al to encapsulate and deliver a therapeutic drug to a patient because the liposome preparation taught by Gregoriadis et al has been demonstrated to **be stable and suitable at least for as an oral-based DNA vaccine**. It is further noted that Unger et al taught explicitly that **the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation**.

Accordingly, claims 1, 3-6, 19-22, 35 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. (US 5,770,222) in view of Gregoriadis et al. (US 7,008,791) for the reasons already set forth above.

Conclusions

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/
Primary Examiner, Art Unit 1633